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Bitemporal versus high-dose unilateral twice-weekly electroconvulsive therapy for depression (EFFECT-Dep): a pragmatic, randomised, non-inferiority trial

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ABSTRACT

Objectives: Electroconvulsive therapy (ECT) is the most effective treatment for severe depression. Previous efficacy studies, using thrice-weekly brief-pulse ECT, reported that high-dose (6x seizure threshold) right unilateral ECT is similar to bitemporal ECT but may have fewer cognitive side-effects. We aimed to assess the effectiveness and cognitive side-effects of twice-weekly moderate-dose (1.5x seizure threshold) bitemporal ECT with high-dose unilateral ECT in real-world practice.

Method: This was a pragmatic, patient- and rater-blinded, non-inferiority trial of patients with major depression (n=138; 63% female; age=56.7[SD=14.8]) in a national ECT service with a six-month follow-up. Participants were independently randomised to bitemporal or high-dose unilateral ECT. The primary outcome was change in the 24-item Hamilton Depression Rating Scale (HAM-D24) after the ECT course; pre-specified non-inferiority margin was 4.0 points. Secondary outcomes included response and remission rates, relapse status after six-months, and cognition.

Results: Sixty-nine patients were assigned to bitemporal ECT and 69 to unilateral ECT. High-dose unilateral ECT was non-inferior to bitemporal ECT regarding HAM-D24 after the ECT course (mean difference=1.2 points in favour of unilateral ECT [95% CI, -1·510 to 3·995]). There were no significant differences for response and remission or six-month relapse status. Recovery-of-orientation was quicker following unilateral ECT (median 19·1 vs 26·4 mins, p<0·001). Unilateral ECT was associated with better % recall of autobiographical information (OR=0·66, p=0·001) that persisted for six months.

Conclusions: Twice-weekly high-dose unilateral ECT is not inferior to bitemporal ECT for depression, and may be preferable because of its better cognitive side-effect profile.

Trial registration: Current Controlled Trials ISRCTN23577151.

INTRODUCTION

Electroconvulsive therapy (ECT) is used to treat severe mental disorders in 1.4 million people annually worldwide, depression being the most common indication in Western countries (1). ECT is the most acutely effective treatment for treatment-resistant, sometimes life-threatening, depression (2, 3). Nevertheless, its use remains limited, mainly because of cognitive side-effects (4), especially concerns about retrograde amnesia (5, 6).

Research on electrode placement has focused on preserving efficacy and minimising side-effects. Based on dosage, right unilateral ECT is less effective than bitemporal ECT (2), the most commonly used electrode placement worldwide (1), but causes less cognitive deficits (7). High-dose is more effective than low-dose ECT but more adversely affects memory (2, 7). However, recent efficacy trials (8-13) have demonstrated that unilateral ECT can be as effective as bitemporal ECT if delivered in high doses at multiples (e.g. 5-8x) of seizure threshold, the minimum charge required to induce the generalised seizure needed for therapeutic effect.

Although unilateral ECT causes fewer cognitive side-effects, the higher charges required to achieve comparable antidepressant efficacy might diminish its cognitive advantage. Relevant trials of brief-pulse (i.e. 1.0-1.5 msec pulse width) ECT have obtained inconsistent results: some show comparable cognitive performance following high-dose (5-8xthreshold) unilateral ECT with reference to moderate-dose (1.0-1.5xthreshold) bitemporal ECT (9, 10, 13) while others demonstrate less cognitive decline following high-dose (6xthreshold) unilateral ECT (8, 11, 12), although the latter studies mostly compared it with higher dose (2.5xthreshold) bitemporal ECT that increases cognitive side-effects (7). None of these studies was designed to determine unilateral non-inferiority for antidepressant effect and most had very limited follow-up. All used thrice-weekly treatment, common practice in the USA where

most of these trials originated, even though this does not result in better outcomes than twice-weekly ECT (14) but is associated with increased cognitive side-effects (15). This limits their generalisability for populations where twice-weekly frequency is common practice, as occurs in many European countries, e.g. Belgium, Ireland, The Netherlands, UK (16, 17). Additionally, none of the previous trials reflected routine practice in that antidepressants were stopped before ECT and all but one (9) required receiving at least eight ECT sessions unless response criteria were met.

To date, no randomised trial has tested whether twice-weekly high-dose (6xthreshold) unilateral ECT is non-inferior to reference (1.5xthreshold) bitemporal ECT nor evaluated its superiority in terms of cognition and retrograde memory preservation over a prolonged follow-up period. We aimed to examine short and long-term effectiveness and cognitive side-effects of high-dose unilateral ECT compared with bitemporal ECT for severe depression in routine practice over six-months.

METHOD

Study design and participants

EFFECT-Dep was a pragmatic, patient- and rater-blinded, two-group, parallel, randomised, non-inferiority trial, with six-month follow-up (18, 19). Participants were all in-patients recruited between May 2008 and October 2012 from St. Patrick's Mental Health Services (http://www.stpatricks.ie/), an independent non-profit organisation that provides national services and runs Ireland's largest ECT clinic, including referrals from public-sector hospitals. Eligible participants were ≥18 years, referred for ECT, met diagnostic criteria for major depressive episode (unipolar or bipolar; Structured Clinical Interview for DSM-IV (20)) and scored ≥21 on the Hamilton Depression Rating Scale-24 (HAM-D24) (21). Exclusion criteria

were: conditions rendering patients unfit for general anaesthesia or ECT; ECT in previous six-months; history of schizophrenia, schizoaffective disorder, neurodegenerative or other neurological disorder; alcohol/substance abuse in previous six-months; involuntary status; inability/refusal to consent. Treatment during the follow-up period was determined by patients in consultation with treating clinicians. This study was approved by the hospital's Research Ethics Committee (012/07) and written informed consent obtained after procedures were fully explained.

Randomisation and masking

After baseline assessments and before the first ECT session, patients were allocated (1:1) to bitemporal or unilateral ECT using an online system by the Clinical Trials Unit, King's College London. Minimisation with variable block sizes ensured group allocation was balanced regarding three stratifiers: age>65 (yes/no); previous ECT (yes/no); referral site (St Patrick's Mental Health Services/St James's Hospital/other hospital). Recruiting researchers electronically submitted participants' identifying number, initials, birthdate, history of ECT, and referral site. Treating clinicians received e-mail notification of randomisation but were not involved in outcome assessments. Allocation was concealed from patients (prepared for receiving both electrode placements), recovery staff, referring clinicians, assessors and trial statistician until completion of final analyses. Success of masking was investigated after end-of-treatment assessments by asking patients and raters to guess the treatment used.

Interventions

Brief-pulse (1.0 msec pulse width; current amplitude 800 mA) ECT was administered twice-weekly (Mecta 5000M device, Mecta Corporation, USA; maximum 1200mC) according to

Royal College of Psychiatrists' guidelines; using methohexital (0.75–1.0 mg/kg) anaesthesia and succinylcholine (0.5–1.0 mg/kg) for muscle relaxation (16, 22). Seizure threshold was established by dose titration at the first session (see Supplemental Material). Subsequent treatments were 1.5xthreshold for bitemporal and 6xthreshold for unilateral (d'Elia placement) ECT. Stimulus charge was titrated upwards as required during the treatment course (22, 23). In line with regular practice, the number of ECT sessions was determined by referring clinicians in consultation with patients, up to 12 sessions in accordance with recommendations of the Irish Mental Health Commission (http://www.mhcirl.ie/Mental_Health_Act_2001/Mental_Health_Commission_Codes_of_Practice/Use_of_ECT_for_Voluntary_Patients/) who publish annual national data on ECT (http://www.mhcirl.ie/Publications/Publications/). Patients continued regular antidepressant treatments. ECT characteristics were recorded: seizure threshold (millicoulomb [mC]); mean stimulus charge (mC) for all sessions and non-titration sessions; motor and EEG seizure durations (seconds); total number of sessions; number of sessions to establish threshold. Time to recovery-of-orientation, i.e. ability to answer 4/5 simple orientation questions (person, place, age, birthdate, day) once breathing spontaneously post-ECT, was recorded after each session(24).

Common adverse physical effects (nausea, headache, muscle aches) were recorded for each session to measure occurrence (Yes/No) within each course. Serious adverse events that required prolonged medical attention or were life-threatening were recorded.

Data were obtained at baseline, within, and soon after (2-4 days) completing the ECT course, and during six-month follow-up. Baseline assessments included the National Adult Reading Test (premorbid IQ), and collection of demographic (age, gender, years-in-education, socio-economic and marital status) and clinical variables: referral reason, treatment-resistance (yes/no; Antidepressant Treatment History Form (25)), current psychotropic medications,

number of previous depressive episodes, current episode duration, presence of psychosis, depression polarity. Baseline Clinical Global Impression (CGI)-severity was rated by referring clinicians.

Primary outcome

The primary outcome was depression severity measured by HAM-D24 after completing the ECT course (end-of-treatment). Inter-rater reliability for HAMD-24 scoring was assessed every six-months; median intraclass correlation agreement was 0.96 (range 0.89-0.98). To classify depression status, HAMD-24 scores were obtained after every second ECT session and one-week after the final session if indicated.

Secondary outcomes

Secondary depression outcomes included HAM-D24 scores at three- and six-month follow-ups; end-of-treatment remission and response status; and relapse status for remitters during six-month follow-up. Remission was defined as ≥60% decrease from baseline HAM-D24 and score ≤10 for two consecutive weeks; response as ≥60% decrease from baseline HAM-D24 and score ≤16; and relapse as HAM-D24 ≥16 for two consecutive weeks. The majority of patients who relapse following successful ECT do so within three-months (26). To monitor relapse, HAM-D24 scores were obtained after end-of-treatment at: 2, 4, 6 and 8 weeks plus 3, 4 and 6 months.

The post-ECT cognitive secondary outcome of main interest, retrograde amnesia measured by the Columbia University Autobiographical Memory Interview-Short Form (27), was prioritised for data collection. Further non-prioritised cognitive outcomes are summarised in Table S2 and included standardised measures of: global cognition (Mini-Mental State

Examination, MMSE); auditory attention and verbal working memory (Digit Spans Forward and Backward); psychomotor speed and executive function (Trail Making Tests A and B); semantic memory (category fluency); verbal learning and delayed recall (Free and Cued Selective Reminding Test); and visuo-spatial functioning and memory (Complex Figures Tests). Alternative versions were used where appropriate. Cognitive outcomes were collected at baseline, end-of-treatment, and three- and six-month follow-ups. These outcomes, as well as the HAM-D24, were similar to ones used to establish efficacy and side-effects of bitemporal ECT (7, 8, 11-13, 16).

Subjective symptoms attributable to ECT were assessed with the Columbia ECT Subjective Side-Effects Schedule, including six items on memory, concentration and orientation for self-rating of cognition (total=18)(28).

Sample size

Based on a large bitemporal ECT series (29), we estimated 69 patients were required per group to have 80% power to demonstrate, using a one-sided equivalence t-test at 5% level, that the mean reduction in HAM-D24 following high-dose unilateral ECT was no more than 4-points (i.e. equivalent to 3-points on HAM-D17, deemed to be clinically relevant (30)) less that achieved using bitemporal ECT.

Statistical analyses

Analyses were on the intention-to-treat principle. ECT measures were summarised by trial arm using relevant descriptive statistics, accompanied by tests of zero group difference where this was not known a priori. We formally compared total numbers of sessions, numbers of sessions to establish seizure threshold (coded "1" or "≥2" sessions) and time to recovery-of-orientation

using regression, logistic regression and regression of log-transformed times respectively. In these regression models, randomisation stratifiers were included as explanatory variables in addition to trial arm.

The primary statistical analysis was assessment of difference in HAM-D24 scores between arms at end-of-treatment. The estimated group difference was supplemented by 95% confidence intervals and this interval compared to the non-inferiority threshold (4 points). A regression model was fitted to end-of-treatment HAMD-24 measures with pre-randomization HAMD-24, trial arm (unilateral/bitemporal) and randomisation stratifiers as covariates. A similar analysis model was assumed for secondary HAM-D24 outcomes at three- and six-months follow-up. Within remitters, relapse during six-month follow-up was compared between arms using logistic regression as above.

The main secondary cognitive outcomes of interest – Autobiographical Memory Interview at end-of-treatment, three- and six-month follow-ups – were analysed using generalised linear models with a binomial distribution and logit-link (31). Post-treatment Autobiographical Memory Interview measures provide the number of baseline items recalled after ECT (27); such "number of items recalled" variables were therefore modelled as arising from binomial distributions, with maximum number of possible recalls set to the number of items obtained at baseline. An overdispersion parameter was introduced to account for recall of individual events being driven by subject characteristics. The covariates of these models were trial arm and randomisation stratifiers.

Similar regression models were employed to describe non-prioritised continuous secondary outcomes – other cognitive tasks and subjective side-effects (now also including baseline values as covariate). Time outcomes (i.e. Trails A and B) were log-transformed before analysis to acknowledge positively-skewed distributions. The same approach was applied for count outcomes displaying positive skewness (Subjective Side-Effects total and cognitive

scores). Group effects for these outcomes were therefore quantified by the ratio of outcome in the bitemporal arm to that in the unilateral arm.

For physical-safety analyses, we assessed proportions of patients who had adverse events by treatment-group and compared proportions using logistic regression modelling as for ECT measures.

Handling of missing data is described in Supplemental Material. We used Stata (version 13) and SPSS 19.0 (IBM Corp, NY) for statistical analyses.

RESULTS

Participant flow

Figure 1 here

Figure 1 shows the trial profile. 475 patients (mean age 62[SD=15.1]; 67.7% female) were referred for ECT during the recruitment period (May 2008 to October 2012), accounting for 32.9% of all ECT referrals in Ireland (n=1480; average age=57.3; 66.5% female). 70 patients, all white Irish, were assigned per group. One patient per trial arm was excluded post-randomisation because they were found not to fulfil eligibility criteria. Comparing the 138 participants to the 113 potentially eligible non-participants, participants were younger (56.7[SD 14.8] vs 63.4[SD 14.3] years; t=3.64, p=0.0001) but did not differ significantly regarding gender (% female: 63% vs 67%; chi-square test, p=0.52) or baseline CGI-severity (5.3[SD 0.7] vs 5.2[SD 0.9] (n=101); U-test z=0.93, p=0.35) and MMSE scores (27.7[SD 2.1] (n=119) vs 27.8[SD 2.5] (n=85); t=-0.27, p=0.79).

All patients adhered to allocated treatment, although five (7.2%) unilateral patients had thresholds >200mC (225mC, N=1; 250mC, N=3; 500mC, N=1) and so could not be treated at fully 6xthreshold. Nearly all participants (N=136; 98.6%) were assessed for primary outcome at end-of-treatment while 82% and 76% were followed-up respectively at three- and six-months.

Treatment guesses were made by patients (119/138) and raters (118/138): 12 patients couldn't guess; 26/56 of the unilateral group and 36/51 in bitemporal group correctly guessed ($\chi 2$=3.27, p=0.07, Kappa=0.17 (low coefficient of beyond-chance agreement)). For raters, 30/57 of guesses for the unilateral group and 36/61 for bitemporal group were correct ($\chi 2$=1.61, p=0.21, Kappa=0.12). Thus masking was successful for patients and raters.

Baseline and treatment characteristics

Summaries of baseline characteristics were comparable between trial arms as would be expected under random allocation (Table 1). Age (56.7[14.8] years), gender (63% female), psychosis-status (21%), bipolarity (23%), baseline HAM-D24 (29.9[6.2]), and depression episode median duration (19.5 weeks) for total sample were similar to previous relevant trials (8, 9, 11-13) and large observational studies (5, 29).

Tables 1 and 2 here

Anaesthesia doses were similar for the two groups (Table 2). In line with previous studies (8-12), we found threshold was lower with unilateral ECT, total stimulus charges were higher in the unilateral group, while seizure durations were similar between groups. 93% of

patients had an adequate seizure in the first session. Although it took fewer sessions to establish threshold in the unilateral group (p=0.002), there was no significant difference between groups for total number of ECT sessions (p=0.26). Median time to recovery-of-orientation following the initial titration-session in the unilateral group was half that of bitemporal group (p<0.001) and this cognitive advantage was maintained, though to a lesser extent, during remainder of the course.

Primary and secondary mood outcomes

Figure 2 here

High-dose unilateral ECT was non-inferior to bitemporal ECT at end-of-treatment. Changes in HAM-D24 scores are illustrated in Figure 2a. The pre-specified non-inferiority margin was no more than -4 points difference at end-of-treatment between bitemporal and unilateral groups (Figure 2b). The predicted difference at end-of-treatment was 1.08 (95% CI -1.67 to 3.84; unilateral N=67, bitemporal N=69). Non-inferiority was evident at both three-month (3.48, 95% CI -0.046 to 7.0; unilateral N=60, bitemporal N=53) and six-month (0.26, 95% CI -3.33 to 3.85; unilateral N=55, bitemporal N=50) follow-ups.

These results translated into similar proportions of responders (unilateral: 42/69 (60.8%); bitemporal: 35/69 (50.7%)) and remitters (unilateral: 32/69 (46.4%); bitemporal: 29/69 (42.0%)) in the two groups at end-of-treatment. The median number of ECT sessions for both responders and remitters was 7 (range 3-12) and was less than for both non-responders and non-remitters at 9 (range 3-12) (for both Mann-Whitney U test, p<0.001). During the six-month follow-up there was no significant difference between proportions of remitters who

relapsed in the unilateral (8/32; 25.0%) and bitemporal (11/29; 37.9%) groups (OR (unilateral/bitemporal)=0.56, 95% CI 0.17 to 1.79, z=0.99, p=0.32).

Cognitive secondary outcomes

Figure 3 here

The cognitive outcome of main interest post-ECT was retrograde amnesia as measured by Autobiographical Memory Interview. Autobiographical memory scores for unilateral (46.9[9.7], N=66) and bitemporal (44.4[10.3], N=64) groups were similar at baseline. The % consistency of recall of baseline memories was lower in the bitemporal group at end-of-treatment (OR=0.66, 95% CI 0.513 to 0.85, p=0.001; unilateral N=64, bitemporal N=64) and this was maintained at follow-up after three-months (OR=0.59, 95% CI 0.45 to 0.78, p<0.001; unilateral N=56, bitemporal N=48) and six-months (OR=0.59, 95% CI 0.45 to 0.79, p<0.001; unilateral N=49, bitemporal N=42) (Figure 3). Distributions of individual % recall consistencies are presented in Table S3.

Assessment completion levels varied for non-prioritised secondary outcomes. End-of-treatment completion rates ranged from 93.5% (category fluency) to 71.7% (verbal learning). Three-month completion rates varied from 62.3% (category fluency) to 47.8% (Trail-Making B), and at six-months from 59.4% (category fluency) to 42.8% (Trail-Making B).

There were few differences between groups for the other cognitive tasks (Table S4). At end-of-treatment the only statistically significant difference was for better performance in the unilateral group on verbal learning for immediate recall (p=0.034) though not delayed recall (p=0.22). There were no differences between groups on these verbal learning and memory tasks at three- and six-month follow-ups. At three-months performance was better in

the unilateral group for both auditory attention (p=0.021) and verbal working memory (p=0.049) but these cognitive advantages were not evident at end-of-treatment or six-month follow-up.

There were no significant differences between groups on the Subjective Side-Effects Schedule for total side-effects at any timepoint (Table S4) although number and severity of side-effects declined substantially over time, probably in line with improved mood (16, 28). However, significantly fewer subjective cognitive side-effects were reported by the unilateral group at end-of-treatment (p=0.02) and after six-months (p=0.025). Thus there were both objective and subjective cognitive advantages for unilateral compared to bitemporal ECT.

Adverse events

There were no differences between unilateral and bitemporal groups for occurrence of headaches (26.5% vs 27.5%; OR=0.93, 95% CI 0.42 to 2.04; z=0.20, p=0.84), nausea (16.2% vs 11.6%; OR=1.54, 95% CI 0.56 to 4.17; z=-0.84, p=0.40) or muscle pain (11.8% vs 8.7%; OR=1.37, 95% CI 0.44 to 4.17; z=-0.55, p=0.58).

Regarding major adverse events, six patients required β-blockers for ECT-related hypertension (unilateral N=4, bitemporal N=2). In the unilateral group: one patient developed laryngospasm with temporary drop in oxygen saturation; one developed tachyarrhythmia necessitating ECT termination; and one attempted suicide during the course. In the bitemporal group: three developed inter-ictal confusion resulting in postponement/termination of ECT; one developed bronchospasm; one required β-blocker for sinus tachycardia; one developed bradyarrhythmia; and one developed a pulmonary embolus after the fifth treatment. None of these events led to trial dropout.

DISCUSSION

Our findings show that twice-weekly high-dose unilateral ECT is non-inferior to bitemporal ECT for severe depression in regular clinical practice, which included continued antidepressant pharmacotherapy, and this was maintained over six-months. The proportions of responders and remitters, as well as relapse rates, are consistent with this. Furthermore, we found high-dose unilateral ECT to be less taxing on autobiographical memory than bitemporal ECT. The unilateral group showed significantly higher autobiographical memory consistency with baseline recall than the bitemporal group at end-of-treatment, and three- and six-month follow-ups. Other cognitive advantages of unilateral ECT included quicker recovery-of-orientation following treatments, better verbal learning at end-of-treatment, and fewer subjective cognitive side-effects. Both forms of ECT were well-tolerated. Numbers of common physical side-effects and serious adverse events were similar in both groups, in line with previous studies reporting harms (12, 32).

Our findings for the primary outcome, HAM-D24, are consistent with results of previous, non-pragmatic, thrice-weekly efficacy trials (8-13). However, the overall remission rate (44.2%) was lower than in some trials (range 46-65%) (8, 9, 11-13) but similar to that in a large community study (46.7%) (33) while the overall six-month relapse rate (31.1%) was at the lower limit reported in a recent meta-analysis of post-ECT relapse (26). These differences most likely reflect the pragmatic nature of our trial, where number of treatments was decided by patients and referring physicians rather than by protocol as well as a naturalistic follow-up, and are unlikely to be related to concomitant use of antidepressants, which may improve ECT efficacy (12). Cognitive outcomes at end-of-treatment were consistent with previous thrice-weekly ECT trials (8, 9, 11, 12). Regarding autobiographical memory, as measured by the Autobiographical Memory Interview, our findings differed only from two previous trials (9, 13) that found both treatments had comparable effects. This might be explained by the higher

stimulus charge used for the unilateral group (8xthreshold) for one trial (9) and/or use of thrice-weekly ECT (9, 13) as both result in larger cognitive deficits.

Strengths and weaknesses

Trial strengths include non-inferiority design, pragmatic attitude, relatively large sample size and adequate power. We showed excellent adherence and end-of-treatment completion rates. Retention at both follow-ups was satisfactory for the primary and main cognitive outcomes and superior to previous relevant trials. Indeed, existing efficacy trials either lacked follow-up (8, 12, 13), had shorter follow-ups (1-2 months) (9, 10) and/or had smaller follow-up samples (19-22 per group) (9, 11). None was designed to test non-inferiority of high-dose unilateral ECT compared to bitemporal ECT. The randomised sample was representative of the general population referred for ECT and similar to potentially eligible non-participants. Our findings, therefore, have good generalisability to countries where twice-weekly ECT is normal practice.

Our study has some limitations. First, we did not include involuntary patients who could not consent due to illness severity (7.4% of referrals) for whom bitemporal ECT may be better(13). Second, other than for autobiographical memory, there are high levels (13-54%) of missing variables for secondary cognitive outcomes at follow-ups. Nevertheless, this study presents the best available evidence of long-term cognitive correlates of high-dose unilateral and bitemporal ECT. A third limitation concerns the Autobiographical Memory Interview. We selected this instrument to situate our trial within existing research evidence as most previous trials used a variant of it (8, 11-13). However, it does not allow quantification of retrograde amnesia attributable directly to ECT even though it is sensitive in detecting differences between treatment allocations on autobiographical memory recall (6, 7, 34, 35). Nevertheless, the present trial shows that high-dose unilateral ECT affects autobiographical memory less than

bitemporal ECT. Fourth, all trial participants were in-patients but this reflected routine practice. Fifth, the relatively lower remission rate may be due to the pragmatic design when compared to other trials (8-13) performed under more stringent, but less clinically general, conditions.

CONCLUSIONS

Our study has important clinical implications. In terms of harms/benefits ratio, high-dose unilateral ECT is non-inferior to bitemporal ECT but showed a better cognitive profile, especially for preserving retrograde personal memories and fewer subjective cognitive side-effects. While there is much interest in other modifications to maintain effectiveness but reduce side-effects, e.g. ultrabrief pulse-width ECT, these require further refinement and characterization for optimisation (36, 37). Our findings justify considering high-dose unilateral ECT as the preferred ECT option for treating depression and may help improve acceptability and availability of this effective treatment.

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FIGURE LEGENDS

Figure 1: Trial profile

HAM-D24=Hamilton Depression Rating Scale-24 item version. ECT=electroconvulsive therapy. SCID-IV=Structured Clinical Interview for DSM-IV. RUL=right unilateral.

Figure 2: Intention-to-treat analyses of primary outcome

(a) Predicted mean HAM-D24 (95% CI) scores for the unilateral and bitemporal ECT groups at end-of-treatment plus three-month and six-month follow-ups. Means are predicted for patients with average baseline outcome value, who are of younger age (≤65 years), referred from St. Patrick's Mental Health Services and have no previous experience of ECT. All analyses were carried out using multiple imputation with 200 imputations (see Statistical Analysis and Supplemental Data). All models used to construct inferences were adjusted for baseline HAM-D24 scores and conditioned on stratifiers. (b) The dashed line is the pre-defined non-inferiority margin (-4 points on the HAM-D24). The green line shows the predicted mean (95% CI) differences in HAM-D24 scores at the same time points as in (a). HAM-D24=Hamilton Depression Rating Scale-24 item version. RUL = right unilateral ECT. Bitemp = bitemporal ECT. EoT=end-of-treatment. M=months.

Figure 3: Autobiographical memory following ECT: recall consistency (%) with baseline scores for unilateral and bitemporal ECT groups

CAMI-SF=Columbia Autobiographical Memory Interview-Short Form. EOT=end-of-treatment. M=months.

TABLE 1: Baseline clinical and demographic characteristics[a]						
Characteristic	**Total sample (N=138)**		**Right unilateral ECT (N=69)**		**Bitemporal ECT (N=69)**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)	56.7	14.8	56.6	15.3	56.8	14.4
Education (years)	13.1	3.4	13.7	3.0	12.6	3.8
HAM-D24	29.9	6.2	30.4	6.1	29.5	6.3
MMSE[a,b]	27.7	2.1	28.0	1.8	27.4	2.4
National Adult Reading Test[a,c]	108.3	6.8	109.2	5.6	107.4	7.8
CGI-S[d]	5.3	0.7	5.4	0.7	5.3	0.7
Number of psychotropic medications	4.2	1.4	4.3	1.3	4.2	1.5
	Median	**Range**	**Median**	**Range**	**Median**	**Range**
Episode duration[e]	19.5	2-104	18.0	4-104	21.0	2-104
Number of previous episodes	4.0	0-23	4.0	0-20	3.0	1-23
	N	**%**	**N**	**%**	**N**	**%**
Female gender	87	63.0	40	58.0	47	68.1
Socio-economic group						
Professional	24	17.4	10	14.5	14	20.3
Managerial or technical	23	16.7	15	21.7	8	11.6
Skilled occupations	36	26.1	23	33.3	13	18.8
Partly skilled occupations	22	15.9	8	11.6	14	20.3
Unskilled occupations	31	22.5	11	15.9	20	29.0
Not specified	2	1.4	2	2.9	0	0.0
Marital status						
Married	76	55.1	38	55.1	38	55.1
Single	35	25.4	17	24.6	18	26.1
Widowed/divorced	25	18.1	12	17.4	13	18.8
Not specified	2	1.4	2	2.9	0	0.0
Bipolar depression	32	23.2	16	23.2	16	23.2
Presence of psychosis	29	21.0	16	23.2	13	18.8
Treatment resistance[f]	99	72.8	45	66.2	54	79.4
History of previous ECT	53	38.4	26	37.7	27	39.1
Primary reason for ECT referral[d]						
Refractory to medication	75	54.3	37	53.6	38	55.1
Rapid response required	57	41.3	29	42.0	28	40.1
Acute suicidality	5	3.6	2	2.9	3	4.3
Physical deterioration	1	0.7	1	1.4	0	0.0
Psychotropic medications						
SSRIs	29	21.0	15	21.7	14	20.3
SNRIs	67	48.6	32	46.4	35	50.7
Tricyclic antidepressants	39	28.3	20	29.0	19	27.5
Tetracyclic antidepressants	6	4.3	6	8.7	0	0.0
Mirtazapine	46	33.3	24	34.8	22	31.9
Agomelatine	2	1.4	1	1.4	1	1.4
Lithium	56	40.6	28	40.6	28	40.6
Anticonvulsants[g]	39	28.3	18	26.1	21	30.4
Benzodiazepines	81	58.7	35	50.7	46	66.7
Antipsychotics	97	70.3	48	69.6	49	71.0

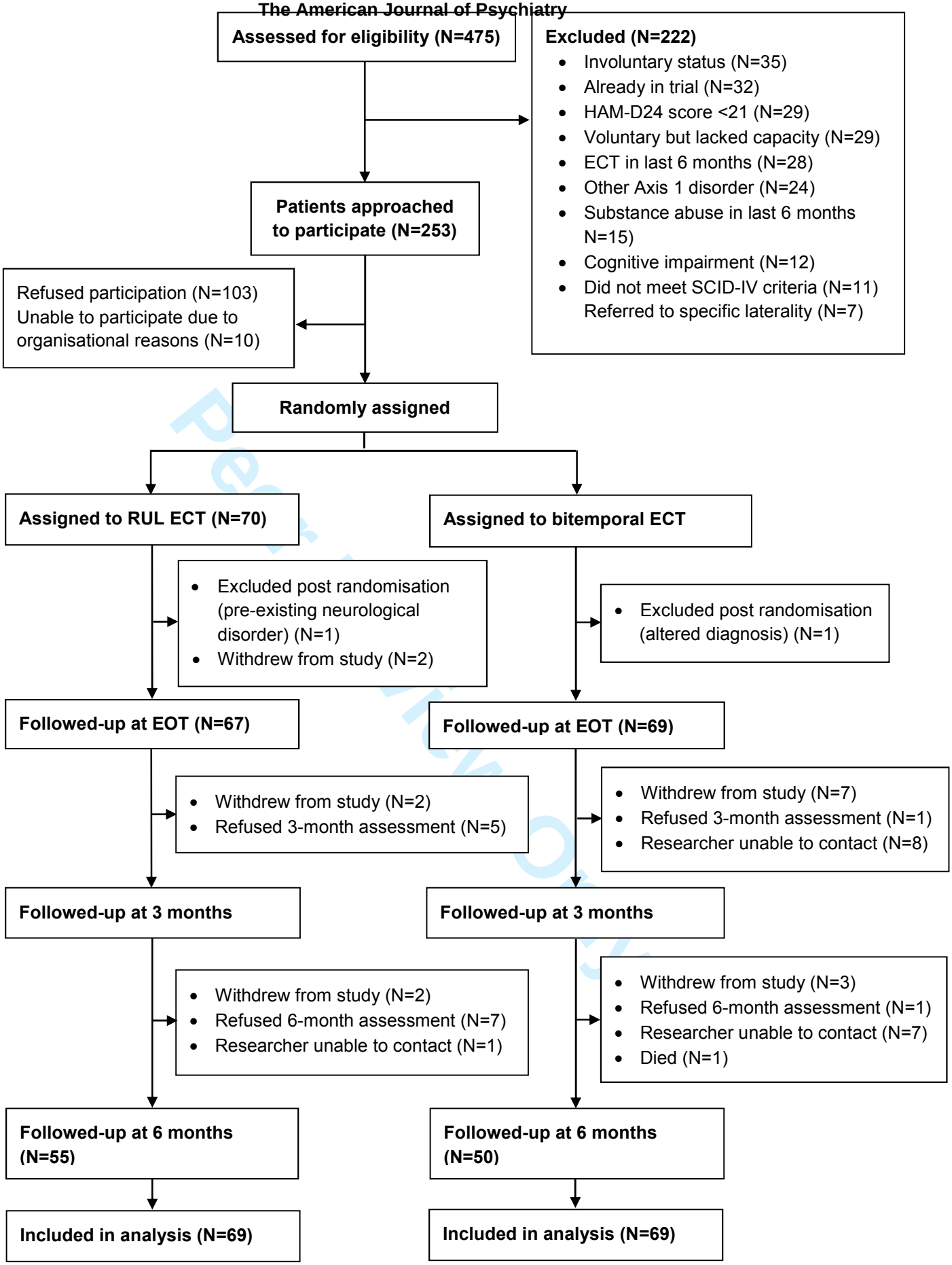
Z-hypnotics	69	50.0	34	49.3	35	50.7
Tryptophan	2	1.4	1	1.4	1	1.4
Buproprion	4	2.9	2	2.9	2	2.9
MAOI	1	0.7	0	0.0	1	1.4
Buspirone	1	0.7	0	0.0	1	1.4

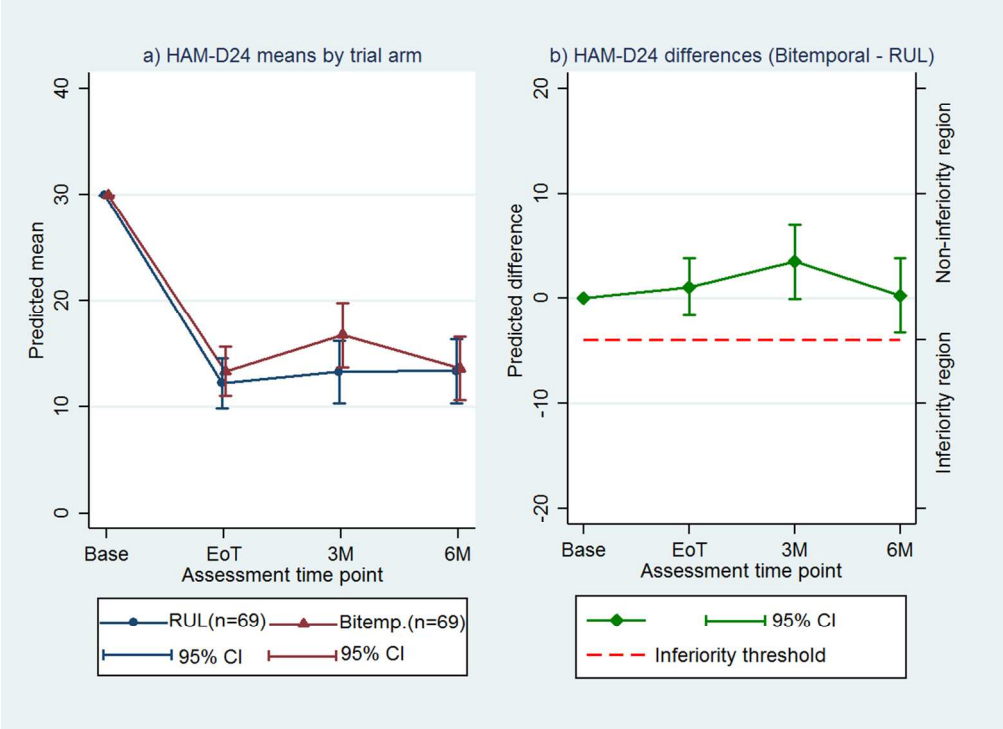
Data are mean (SD) or N (%), unless otherwise indicated.
[a]Data not available for all participants.
[b]N=119 (59 right unilateral, 60 bitemporal)
[c]N=112 (54 right-unilateral, 58 bitemporal)
[d]As recorded by referring physician.
[e]Capped at 104 weeks.
[f]Treatment resistance was based on the Antidepressant Treatment History Form, N=136.
[g]Anticonvulsants include lamotrigine, sodium valproate and pregabalin prescribed as mood stabilisers or anxiolytic.
HAM-D24=24-item Hamilton Depression Rating Scale. MMSE=Mini-Mental State Examination. CGI-S=Clinical Global Impression-Severity Scale. SSRIs=Selective serotonin reuptake inhibitors. SNRIs= Serotonin and Noradrenaline Reuptake Inhibitors. MAOI=Monoamine Oxidase Inhibitor.

TABLE 2: ECT session measures

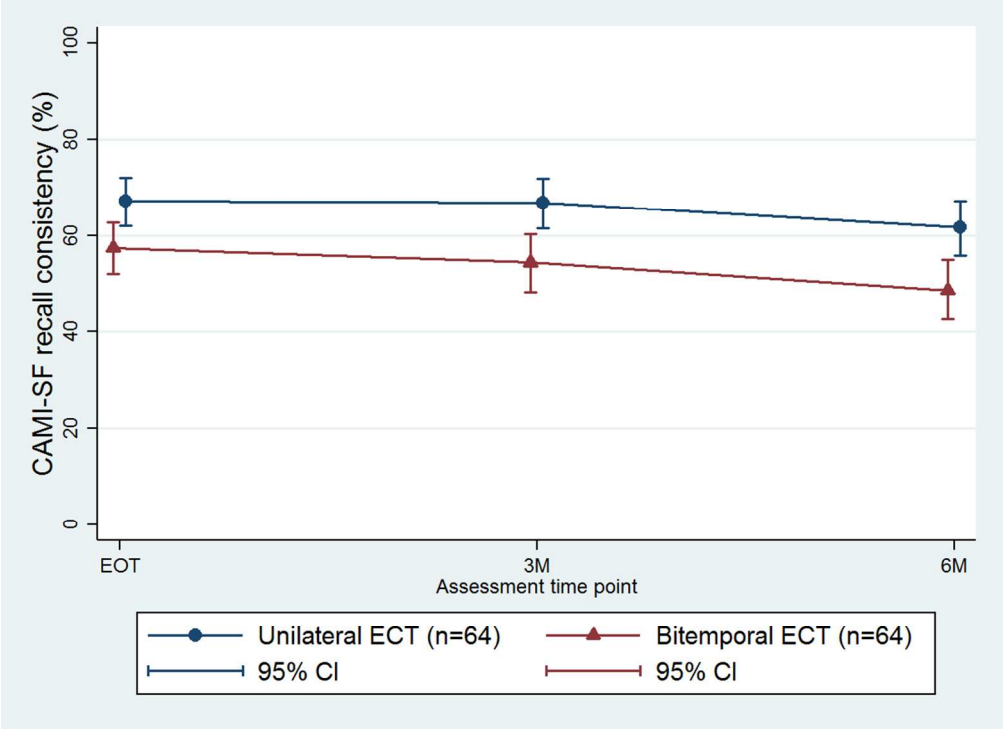
	Right unilateral ECT[a] (N=69)		Bitemporal ECT (N=69)		Formal test[b]
	Mean	**SD**	**Mean**	**SD**	
ECT treatment characteristics					
Anaesthesia[c]					
Methohexitone (mg/kg)	1.1	0.2	1.0	0.2	NA
Suxamethonium (mg/kg)	0.8	0.2	0.8	0.2	NA
Stimulus charge (mC), all sessions	620.3	223.5	368.1	192.0	NA
Stimulus charge (mC), non-titration sessions[d]	741.6	275.6	403.5	207.6	NA
Total number of sessions	7.8	2.5	8.3	2.4	$t(131)=1.13$, $p=0.26$
	Median	**Range**	**Median**	**Range**	
Initial seizure threshold (mC)	75	50-500	150	50-500	NA
Motor seizure duration (s)	28	12-55	28	14-63	NA
EEG seizure duration	42	17-87	40	16-116	NA
	Percentage (%)				
Number of sessions to establish the seizure threshold					
1 session	81		56		$z=3.07$, $p=0.002$
2 sessions	18		41		
3 sessions	1		3		
	Median	**Range**	**Median**	**Range**	
Recovery of orientation[e]					
Time to recovery (mins), initial titration session	10	5-60	20	5-60	$t(130)=6.82$, $p<0{\cdot}001$[f]
Time to recovery (mins), non-titration sessions[g]	19.1	10-55	26.4	10-60	$t(130)=3.88$, $p<0{\cdot}001$[f]

Data are mean (SD), unless otherwise indicated.
[a]Data not available for all participants (N=67-68).
[b]All models used to construct inferences were conditioned on stratifiers.
[c]Six patients received propofol during their ECT course at standard doses due to temporary shortage of methohexital, four in the bitemporal group and two in the unilateral group.
[d]A mean time was estimated for all sessions following the definite establishment of the seizure threshold.
[e]Recovery of orientation was defined as correctly answering 4/5 reorientation questions.
[f]Formal inferences carried out after log-transformation.
[g]A mean time was estimated for all sessions following the definite establishment of the seizure threshold.
NA=not attempted. mC=millicoulombs. EEG=electroencephalogram.


Assessed for eligibility (N=475)
Excluded (N=222)
Involuntary status (N=35)
Already in trial (N=32)
HAM-D24 score <21 (N=29)
Voluntary but lacked capacity (N=29)
ECT in last 6 months (N=28)
Other Axis 1 disorder (N=24)
Substance abuse in last 6 months N=15)
Cognitive impairment (N=12)
Did not meet SCID-IV criteria (N=11)
Referred to specific laterality (N=7)
Patients approached to participate (N=253)
Refused participation (N=103)
Unable to participate due to organisational reasons (N=10)
Randomly assigned
Assigned to RUL ECT (N=70)
Assigned to bitemporal ECT
Excluded post randomisation (pre-existing neurological disorder) (N=1)
Withdrew from study (N=2)
Excluded post randomisation (altered diagnosis) (N=1)
Followed-up at EOT (N=67)
Followed-up at EOT (N=69)
Withdrew from study (N=2)
Refused 3-month assessment (N=5)
Withdrew from study (N=7)
Refused 3-month assessment (N=1)
Researcher unable to contact (N=8)
Followed-up at 3 months
Followed-up at 3 months
Withdrew from study (N=2)
Refused 6-month assessment (N=7)
Researcher unable to contact (N=1)
Withdrew from study (N=3)
Refused 6-month assessment (N=1)
Researcher unable to contact (N=7)
Died (N=1)
Followed-up at 6 months (N=55)
Followed-up at 6 months (N=50)
Included in analysis (N=69)
Included in analysis (N=69)



Intention-to-treat analyses of primary outcome
425x309mm (72 x 72 DPI)



Autobiographical memory following ECT: recall consistency (%) with baseline scores for unilateral and bitemporal ECT groups
425x309mm (72 x 72 DPI)

Bitemporal versus high-dose unilateral twice-weekly electroconvulsive therapy for depression (EFFECT-Dep): a pragmatic, randomised, non-inferiority trial

Supplemental Material

ECT DOSING PROCEDURES

Brief-pulse (1.0 msec pulse width; current amplitude 800 mA) ECT was administered with hand-held electrodes using the Mecta 5000M device (Mecta Corporation, USA; maximum 1200mC). Methohexital (0.75–1.0 mg/kg) was used for anaesthesia and succinylcholine (0.5–1.0 mg/kg) for muscle relaxation. Patients were oxygenated during the procedure with 100% O2 under positive pressure and were monitored for blood pressure, heart rate and rhythm, pulse oximetry and capnography. Seizure duration was measured by observation of motor activity and electroencephalogram (EEG).

Table S1 Stimulus titration and dosing procedures

		Suprathreshold treatment dose (mC)	
Level	Threshold (mC)	Bitemporal (1.5x)	Right unilateral (6x)
1	25	50	150
2	50	75	300
3	75	125	450
4	100	150	600
5	150	225	900
6	250	375	1200
7	350	550	1200
8	500	750	1200
9	750	1000	1200

Empirical dose titration was used to establish the seizure threshold in the first ECT session (1, 2). The seizure threshold was defined as the lowest stimulus charge that produced an adequate seizure, i.e. a generalised tonic/clonic seizure lasting ≥15 seconds from the end of the stimulus, or an electroencephalogram (EEG) record of polyspike followed by 3 Hz spike-and-wave activity lasting ≥25 seconds. The titration procedure is shown in Table S1

and began at the lowest dose of 25 mC. Several factors are known to affect seizure threshold, including older age (>65 years), male gender, use of benzodiazepines and anticonvulsant drugs, and bitemporal electrode placement (3). The presence of any of these factors was incorporated into the dose titration algorithm to tailor the process to the individual patient by beginning at one level higher for each one of these factors when present. For example, in the titration procedure shown in Table S1, the initial stimulus dose for a young adult female undergoing unilateral ECT would be at the lowest level, i.e. 25 mC. However, if she was over 65 years old and taking regular benzodiazepines, the initial stimulus dose would be increased by two levels up to 75 mC.

Patients were stimulated at the appropriate initial level. If an adequate seizure was not produced, then the patient was restimulated one level higher (see Table S1). There was an interval of at least 30 seconds before each restimulation. If an adequate seizure was still not produced after the second attempt, and anaesthetic conditions permitted, the patient was restimulated for the second time at another two levels higher, i.e. one level was skipped. If in the first session a third stimulation was required and resulted in an adequate seizure, the seizure threshold could have been either the dose used or the previous (i.e. skipped) level. Therefore, the second session began with the skipped dose level to clarify the seizure threshold.

Once the seizure threshold was established, subsequent treatments were given at 1.5xthreshold for bitemporal and 6xthreshold for unilateral (d'Elia placement) ECT. Seizure threshold can substantially rise over the course of ECT and this may be manifested in a progressive shortening in seizure duration. The aim of the treatment is to ensure that the dose clearly remains suprathreshold (2). Therefore, if the EEG seizure duration fell by >20% relative to the second session then the initial stimulus dose was raised in the next session by

one level (see Table S1). This new level was adopted as the initial dose for subsequent sessions.

HANDLING OF MISSING DATA

In the presence of missing data, the resulting (maximum likelihood) estimators of group effects on outcome variables are valid provided that missing data-generating mechanisms are Missing At Random (MAR), which here implies that the probability of the outcome being unobserved at the respective post treatment time point depends only on covariates included in the analysis model. Such a MAR assumption might not be realistic and violations of the assumption could lead to biased effectiveness estimates, in particular for non-prioritised secondary outcomes. To base analyses on less restrictive MAR assumptions, we employed multiple imputation (MI). This allowed us to include additional variables (including post randomisation variables) in the imputation step of the MI procedure without having to condition on them in the analysis model. The approach relaxed the MAR assumption to also allow these variables to be predictive of missing outcome and thus avoid bias (4). Specifically, the following types of variables were included in the imputation step: (i) outcome measures at all available time points; (ii) covariates of the analysis model; (iii) known prognostic variables (treatment resistance(5, 6), psychosis(7)); (iv) HDRS-24 at any time point since ability to complete questionnaires may be affected by current depression severity; (v) additional baseline variables detected empirically to predict missingness of respective 6-month outcomes (see later Results); (vi) CAMI-SF at end-of-treatment if this prioritised outcome was found to be predictive of any outcome missingness (8).

Regarding (v) and (vi), we ran a series of binary logistic regressions for observing values of HDRS-24, CAMI-SF, Trail-Making B and FCSRT immediate recall at six-months.

Poor end-of-treatment CAMI-SF performance predicted missingness of both HDRS-24 and CAMI-SF at six-months and was included in all imputation models. With regard to non-prioritised outcomes, poorer performance on category fluency and better performance on FCSRT immediate recall at baseline predicted missingness respectively in Trail-Making B and FCSRT immediate recall and these two variables were also included in the imputation models for these outcomes.

Imputation by chained equations was carried out using Stata's ice command with the number of imputations set to 200. Steps were taken to ensure imputed values lay within limited scale ranges and respected the discrete nature of some scales. In addition, distributions of imputed values were always compared with those of respective observed values to check that imputed values appeared realistic. (Further technical information regarding imputation procedures can be requested from the authors.) Where missing values were present in an outcome we always report findings from the multiple imputation analysis. For the prioritised outcomes (HDRS-24, CAMI-SF), where the amount of missingness was relatively small, we also compared MI results with complete-case analysis results and found these to be very similar (details not reported.)

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Table S2 Neurocognitive test battery and associated references	
Test	**Reference**
Mini-mental state examination	Folstein MF, Folstein SE, McHugh PR: "Mini mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189-198
National Adult Reading Test	Nelson HE, Willison I: National Adult Reading Test (NART). Windsor, NFER Nelson, 1991
Digit Span (WAIS-III)	Wechsler D: Wechsler Adult Intelligence Scale-Third Edition (WAIS-III). San Antonio, The Psychological Corporation, 1997
Trails Making Tests A and B	Reitan RM Wolfson, D: The Halstead–Reitan Neuropsycholgical Test Battery: Therapy and clinical interpretation. Tucson, AZ, Neuropsychological Press, 1985
Category fluency	Lezak MD, Howieson DB, Biegler ED, Tranel D: Neuropsychological assessment. 5th ed. New York, Oxford Univerity Press, 2012
Free and Cued Selective Reminding Test	Van der Linden M, GREMEM: Memory disorders assessment - four episodic memory tests with normative data. Marseille, Solal, 2004
Complex Figures Test	Strauss E, Sherman EMS, Spreen O: Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. 3rd ed. New York, Oxford University Press, 2006, pp. 811-841 Versions: (1) Rey-Osterrieth, Form A, (2) Rey-Osterrieth, Form B, (3) Medical College of Georgia Complex Figure 1; (4) Medical College of Georgia Complex Figure 2

TABLE S3: Distribution of % autobiographical memory recall consistency scores on the Columbia Autobiographical Memory Interview – Short Form according to treatment allocation

	Bitemporal electrode placement	Right unilateral electrode placement
	End-of-treatment	
Minimum	0	27
Maximum	100	93
25th Percentile	46.25	54.25
50th Percentile	55.00	71.00
75th Percentile	69.00	80.75
	3-months follow-up	
Minimum	11	20
Maximum	100	93
25th Percentile	41.50	59.25
50th Percentile	56.50	68.00
75th Percentile	67.75	76.75
	6-months follow-up	
Minimum	28	13
Maximum	95	92
25th Percentile	42.00	53.5
50th Percentile	50.00	65.00
75th Percentile	64.25	78.50

TABLE S4: Results of analyses of cognitive outcomes by post treatment time point						
Cognitive tasks			**Comparison of randomisation groups[a]**			
	Predicted mean[b] RUL (N=69)	**Predicted mean[b] Bitemporal (N=69)**	**Estimated difference in means**		**Statistical significance test**	
			BT-RUL	**95% CI**	**z**	**p**
Global cognitive status: MMSE						
Baseline (sample average)	27.7 (N=59)	27.7 (N=60)				
EOT	27.8 (N=62)	27.4 (N=63)	-0.4	-1.2 to 0.4	-0.93	0.35
3 months	27.9 (N=45)	28.1 (N=31)	0.2	-0.6 to 1.0	0.44	0.66
6 months	28.2 (N=38)	28.1 (N=32)	-0.1	-1.1 to 1.0	-0.12	0.90
Psychomotor speed: TMT-A[c]						
Baseline (sample average)	51.4 (N=49)	51.4 (N=54)				
EOT	53.1 (N=54)	47.9 (N=59)	0.9	0.8 to 1.0	-1.52	0.13
3 months	44.1 (N=40)	43.8 (N=28)	1.0	0.8 to 1.2	-0.07	0.94
6 months	41.0 (N=34)	43.1 (N=30)	1.1	0.9 to 1.3	0.52	0.61
Auditory attention: Digit span forward						
Baseline (sample average)	8.0 (N=53)	8.0 (N=52)				
EOT	8.8 (N=55)	8.1 (N=58)	-0.7	-1.5 to 0.2	-1.51	0.14
3 months	8.8 (N=41)	7.7 (N=30)	-1.2	-2.1 to -0.2	-2.36	0.02
6 months	9.3 (N=38)	8.4 (N=29)	-0.8	-1.8 to 0.1	-1.76	0.08
Verbal working memory: Digit span backward						
Baseline (sample average)	5.7 (N=53)	5.7 (N=52)				
EOT	5.9 (N=55)	5.8 (N=58)	-0.04	-0.9 to 0.8	0.08	0.93
3 months	6.4 (N=41)	5.6 (N=30)	-0.8	-1.6 to 0.0	2.01	0.05
6 months	7.0 (N=37)	6.3 (N=29)	-0.6	-1.7 to 0.5	-1.16	0.25
Verbal learning: FCSRT immediate recall						
Baseline (sample average)	24.9 (N=47)	24.9 (N=48)				
EOT	25.7 (N=49)	22.5 (N=50)	-3.2	-6.1 to -0.2	-2.15	0.03
3 months	27.3 (N=36)	26.7 (N=31)	-0.6	-3.5 to 2.4	-0.40	0.69
6 months	28.5 (N=33)	27.6 (N=28)	-0.9	-4.9 to 3.0	-0.46	0.65
Verbal delayed memory: FCSRT delayed recall						
Baseline (sample average)	9.6 (N=47)	9.6 (N=47)				
EOT	8.5 (N=49)	7.7 (N=49)	-0.8	-2.1 to 0.5	-1.24	0.22
3 months	9.3 (N=36)	9.2 (N=31)	-0.2	-1.5 to 1.2	-0.23	0.82
6 months	9.6 (N=32)	9.2 (N=28)	-0.4	-1.8 to 1.05	-0.53	0.60
Visuo-spatial functioning: CFT copy						
Baseline (sample average)	26.4 (N=46)	26.4 (N=45)				
EOT	28.9 (N=51)	29.2 (N=54)	0.3	-1.4 to 2.1	0.37	0.71

3 months	30.9 (N=39)	31.0 (N=31)	0.2	-1.5 to 1.8	0.19	0.85
6 months	30.3 (N=33)	30.2(N=29)	-0.1	-1.8 to 1.6	-0.09	0.93
Visual memory: CFT delayed recall						
Baseline (sample average)	11.3 (N=44)	11.3 (N=40)				
EOT	14.8 (N=50)	14.1 (N=49)	-0.7	-2.9 to 1.5	-0.65	0.52
3 months	19.2 (N=39)	18.0 (N=28)	-1.2	-3.9 to 1.5	-0.89	0.38
6 months	19.2 (N=32)	18.1 (N=28)	-1.1	-4.1 to 2.0	-0.70	0.49
Semantic memory: Category fluency						
Baseline (sample average)	14.0 (N=60)	14.0 (N=59)				
EOT	12.7 (N=65)	12.1 (N=64)	-0.6	-2.3 to 1.0	-0.77	0.44
3 months	14.1 (N=53)	13.8 (N=33)	-0.3	-2.3 to 1.8	-0.28	0.78
6 months	14.4 (N=46)	13.5 (N=36)	-0.9	-2.8 to 1.0	-0.93	0.36
Executive functioning: TMT-B[c]						
Baseline (sample average)	117.9 (N=46)	117.9 (N=50)				
EOT	103.8 (N=47)	107.7 (N=54)	1.0	0.9 to 1.2	0.42	0.67
3 months	87.0 (N=39)	93.1 (N=27)	1.1	0.9 to 1.3	0.66	0.51
6 months	84.1 (N=32)	97.2 (N=27)	1.2	0.9 to 1.5	1.16	0.25
Total side-effects: CSSES total score[c]						
Baseline (sample average)	22.4 (N=50)	22.4 (N=48)				
EOT	14.2 (N=63)	17.3 (N=62)	1.2	0.9 to 1.6	1.44	0.15
3 months	12.5 (N=47)	13.4 (N=32)	1.1	0.7 to 1.6	0.38	0.71
6 months	8.7 (N=39)	12.1 (N=38)	1.4	0.9 to 2.1	1.49	0.14
Cognitive side-effects: CSSES cognitive score[c]						
Baseline (sample average)	5.0 (N=52)	5.0 (N=48)				
EOT	3.8 (N=63)	5.5 (N=62)	1.4	1.1 to 2.0	2.32	0.02
3 months	4.2 N=47)	4.9 (N=32)	1.2	0.8 to 1.6	0.83	0.41
6 months	3.3 (N=39)	4.9 (N=38)	1.5	1.1 to 2.1	2.24	0.03

These scales were not prioritized and hence are subject to missingness.
[a]All analyses were carried out using multiple imputation with 200 imputations (see Supplemental Material).
[b]Means are predicted for patients with average baseline outcome value, who are of younger age (≤65 years), referred from St. Patrick's Mental Health Services and have no previous experience of ECT.
[c]Analysis carried out on the log-scale, means back-transformed and effect estimates representing ratios (Bitemporal/Right unilateral).
RUL=right unilateral ECT. MMSE=Mini-Mental State Examination. TMT=Trail Making Test (versions A and B). FCSRT= Free and Cued Selective Recall Test. CFT=Complex Figure Test. CSSES=Columbia ECT Subjective Side-Effects Schedule.